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JACC STATE-OF-THE-ART REVIEW

Sudden Death in Obesity

Mechanisms and Management

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ABSTRACT

In recent decades, the prevalence of obesity has increased significantly, leading to an epidemic at the global level. Obesity is associated with various metabolic alterations and increases the risk of cardiovascular disease. The most devastating manifestation of cardiovascular disease is sudden cardiac death (SCD), leading to substantial years of potential life lost worldwide. Obesity-related SCD is an increasingly important public health problem and warrants a specific investigative focus on improved risk stratification and prevention. In this review, we summarize the current evidence regarding management of SCD in obesity and discuss knowledge gaps as well as future directions in this field. (JACC. 2024;84:2308-2324) © 2024 by the American College of Cardiology Foundation.

BACKGROUND AND INTRODUCTION

DEFINITIONS. Sudden cardiac death. Sudden cardiac death (SCD) is generally defined as death due to cardiac causes that occurs suddenly and unexpectedly.[1] SCD has been estimated to account for about one-half of all cardiovascular deaths,[2] with an estimated annual U.S. incidence of >325,000.[3] The critical event is sudden cardiac arrest (SCA), which is mostly lethal because only about 10% survive.[4] Therefore, prediction and prevention of SCA are the most important measures to reduce premature mortality from SCD.

In the vast majority of individuals, SCD is a multifactorial and complex event that can involve multiple underlying substrates and maintainers of lethal ventricular arrhythmias (VAs) (eg, coronary artery disease [CAD], cardiac hypertrophy) and acute triggers (eg, ischemia, hypoxia, and electrolyte imbalance).[5,6] The most important underlying substrate for SCD in the general population is CAD, accounting for approximately 70% to 80% of all subjects.[7-9] SCD may strike at any age, but the average age of SCD victims ranges between 60 to 70 years, and the prevalence of CAD starts to increase in the fourth decade.[7,8] Among younger SCD victims, inherited cardiomyopathies, arrhythmia syndromes, and structurally normal findings prevail in postmortem investigations.[10]

Obesity. Obesity is a condition where there is an excessive accumulation of body fat. In the majority of individuals, obesity develops because of a chronic mismatch in energy intake and consumption and is most often defined as body mass index (BMI) ≥30 kg/m^2. Severe obesity (class 2) and morbid obesity (class 3) are defined as BMI ≥35 kg/m^2 and BMI ≥40 kg/m^2, respectively.[11] However, BMI does not directly measure body composition and in some instances, high BMI may result from high muscle mass or water retention. Body fat is usually distributed around visceral organs or subcutaneously, and visceral fat is metabolically more active and more strongly associated with increased overall mortality,[12] as well as SCD.[13] More specific measurements for

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estimating visceral fat may be waist circumference, waist-to-hip ratio (WHR), and sagittal abdominal diameter (SAD). The amount of body fat can also be assessed with various body composition measurements (eg, bioimpedance), but the current literature lacks comprehensive studies using such measures in assessing the risk of SCD.

In 1998, the National Institutes of Health classified obesity as a complex multifactorial chronic disease.[14] Obesity is associated with lower life expectancy of approximately 4 years,[15] and more than two-thirds of obesity-related deaths are due to cardiovascular causes (**Figure 1**).[11] According to the Global Burden of Disease, over 4 million people die annually because of being overweight or obese.[16] During the last 2 decades, the prevalence of obesity has increased from 30.5% to 41.9% among adults aged 20 and over in the United States.[17] Given this high prevalence, obesity is associated with a high population-attributable fraction of cardiovascular diseases and SCD.[18]

EPIDEMIOLOGICAL EVIDENCE LINKING OBESITY TO SCD

BMI AND SCD. Several epidemiological studies have investigated the relationship between BMI and the risk of SCD. The balance of evidence suggests a significantly increased risk of SCD associated with obesity. A meta-analysis demonstrated that every 5-unit increment in BMI is associated with a 16% increased risk of SCD.[19] The risk is highest among those with high BMI but is also increased among those with low BMI, creating a J-shape association between BMI and the risk of SCD.

OBESITY AND THE PROPORTIONAL RISK OF SCD. Early studies reported that the proportion of SCD in CAD-related deaths was increased in obese individuals[20,21] but findings in more recent studies have been mixed. The proportional risk of SCD and obesity has been investigated in heart failure (HF). A recent study developed prognostic models for arrhythmic and nonarrhythmic mortality among 4,531 patients with left ventricular dysfunction due to CAD (enrolled in the MADIT [Multicenter Automatic Defibrillator Implantation Trial]) and found that low BMI predicted nonarrhythmic mortality more than arrhythmic mortality.[22] Somewhat similar results were found in a cohort of 9,885 HF patients without implantable cardioverter-defibrillators (ICDs), in which higher BMI was independently associated with a greater proportional risk of sudden death.[23] However, another report from the general population suggested that the risk for nonsudden cardiac mortality is similarly increased in obesity.[24] This finding is supported by data from the 1986 National Mortality Followback Survey and the U.S. Bureau of the Census, in which there were no differences in BMI between SCD and non-SCD CAD deaths.[25] Because the prevalence of obesity continues to rise, more studies using consistent definitions of obesity are needed.

VISCERAL OBESITY. When compared to BMI, visceral obesity has been associated more strongly with increased risk of SCD. A meta-analysis by Aune et al[19] found that a 0.1-U increase in WHR was associated with an 82% increased risk of SCD. Increased SCD risk in visceral obesity has been demonstrated in both sexes. In the Paris Prospective Study,[26] the risk of SCD increased proportionally with SAD level, and individuals in the highest SAD quintile had a 2.6-fold higher risk of SCD in comparison to those in the lowest SAD quintile. Similarly, a study by Bertoia et al[27] investigated 161,808 women from across the United States and found that the highest WHR quartile was associated with a 73% increased risk of SCD. WHR had the greatest population-attributable fraction for SCD along with hypertension and myocardial infarction (MI). Data from the Nurses' Health Study suggested that abdominal obesity is associated with elevated cardiovascular mortality even among those with normal BMI.[28]

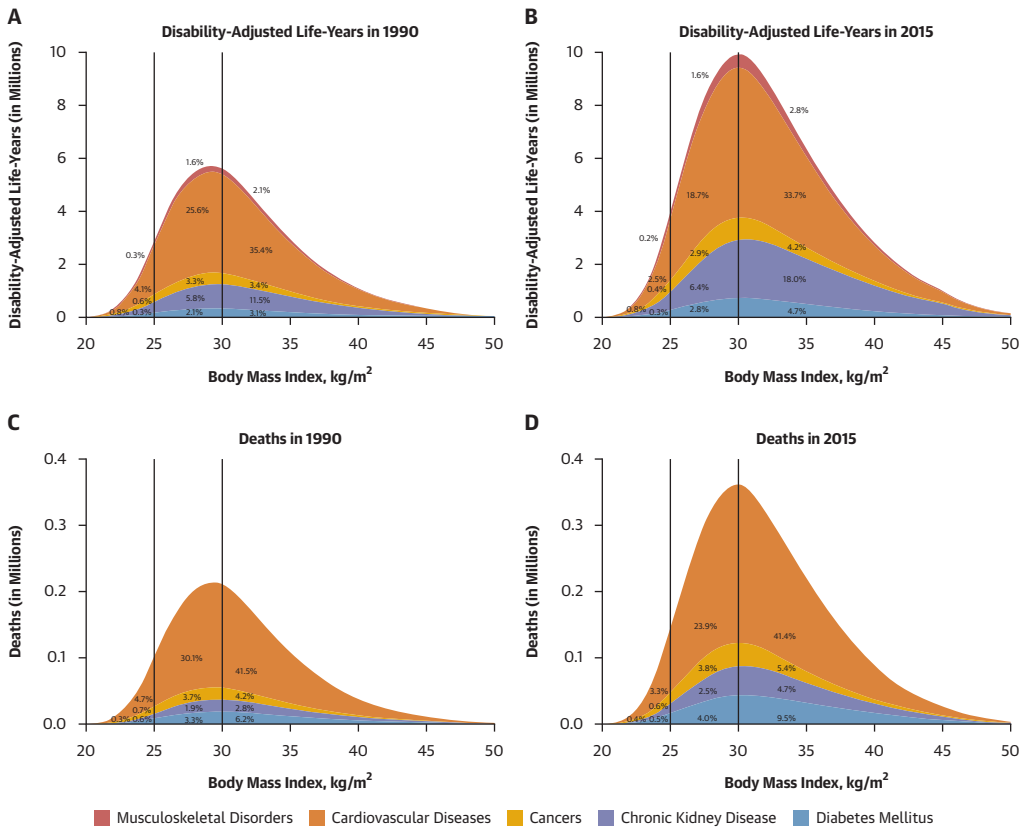
OBESITY PARADOX. The obesity paradox refers to several observations that have demonstrated that in the elderly and patients with chronic diseases (eg, heart failure or CAD), overweight or mild obesity may be protective and is associated with higher survival.[29] Primary prevention ICD is currently recommended for HF patients with ejection fraction ≤35%, and the obesity paradox has also been shown to apply in HF patients with an ICD.[30] The reasons for the obesity paradox are not fully clear. Potential explanations include lead time bias (patients with obesity may develop cardiac disease earlier in their lifetime), cardiac cachexia (patients with low BMI and unintentional weight loss have a high mortality rate), and lower comorbidity burden, which may result from an earlier age at the time of cardiac disease diagnosis.[11]

In the sudden cardiac arrest setting, obesity might influence both underlying etiologies and presenting rhythm, creating special challenges that impact on

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
CAD = coronary artery disease
CPAP = continuous positive airway pressure
ECG = electrocardiography
GLP = glucagon-like peptide
HF = heart failure
ICD = implantable cardioverter-defibrillator
MI = myocardial infarction
OSA = obstructive sleep apnea
SAD = sagittal abdominal diameter
SCA = sudden cardiac arrest
SCD = sudden cardiac death
VA = ventricular arrhythmia
WHR = waist-to-hip ratio

FIGURE 1 Global BMI-Related Mortality and Disability-Adjusted Life-Years 1990-2015



The figure shows the number of deaths and disability-adjusted life-years in adults that are related to a high body mass index (BMI) in 1990 and 2015 according to the BMI level and cause. (A) BMI-related disability-adjusted life-years in 1990. (B) BMI-related disability-adjusted life-years in 2015. (C) BMI-related mortality in 1990. (D) BMI-related mortality in 2015. BMI threshold for overweight (25-29 kg/m^2) and obesity (>30 kg/m^2) are marked with the vertical lines. Reproduced with permission from GBD 2015 Obesity Collaborators et al.[18]

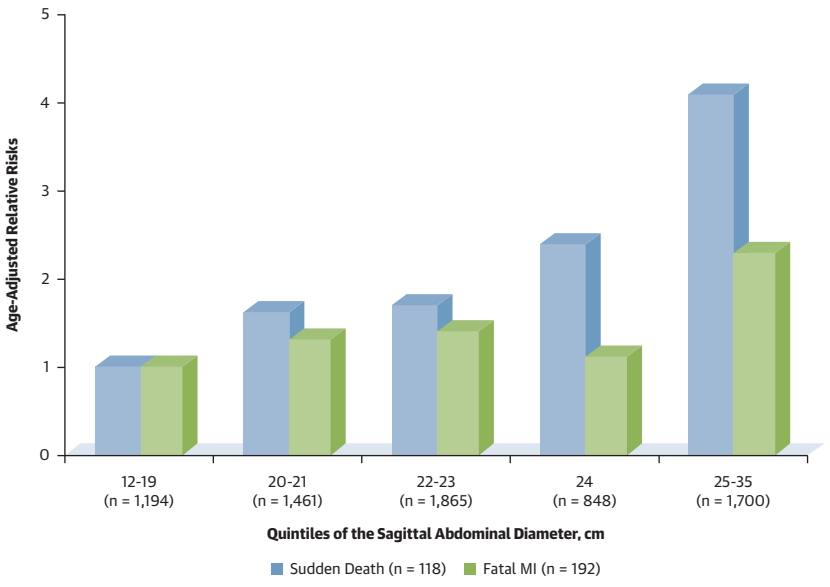
resuscitation efforts and survival rates. Some studies have found that patients with obesity have a worse prognosis in out-of-hospital cardiac arrest.[31,32] For example, data from the Swedish Registry of Cardiopulmonary Resuscitation showed that obesity was associated with a 31% decrease in survival, which further decreased by 45% when obesity was accompanied by diabetes.[32] However, other studies have found different results, and there is no clear evidence regarding whether obesity affects the chances of survival after cardiac arrest.[33,34]

CLINICAL ANTECEDENTS OF OBESITY-RELATED SCD

Obesity increases the risk of traditional cardiovascular risk factors, which are also important mediators of SCD risk. The risk of type 2 diabetes is increased by approximately 10-fold,[35-37] CAD by ~5-fold,[29,35,38] hypertension by ~3-fold,[38,39] and dyslipidemia by ~2-fold[39] in obese patients. More than one-half of obese patients have metabolic syndrome,[40-42] which is defined as having ≥3 metabolic syndrome components (high blood pressure, high plasma triglycerides, low high-density lipoprotein cholesterol, high fasting blood glucose, and abdominal obesity).[43] Although metabolic syndrome is usually treated as a dichotomous variable, the relationship between metabolic syndrome components and cardiovascular disease is more likely to be a continuum, with a higher burden of component conditions corresponding to a higher risk of SCD.[44]

IS OBESITY AN INDEPENDENT RISK MARKER FOR SCD? Despite the confounding effect of metabolic abnormalities, obesity has also been associated with

FIGURE 2 **Relationships Among Sagittal Abdominal Diameter, Sudden Death, and Fatal MI**



Data from the Paris Prospective Study showed that abdominal obesity increases the risk of sudden cardiac death regardless of body mass index, and the association was stronger between abdominal obesity and sudden cardiac death than between abdominal obesity and fatal myocardial infarction (MI). Reproduced with permission from Empana et al.[26]

an increased risk of SCD independently from other conventional cardiovascular risk factors. In the ARIC (Atherosclerosis Risk In Communities Study), abdominal obesity was associated with a 2-fold increased risk of SCD independently from hypertension, diabetes, abnormal lipid levels, prevalent CAD/HF, resting heart rate, and electrocardiography (ECG)-left ventricular hypertrophy.[13] Another study of a general population sample of 10,543 middle-aged subjects found that BMI ≥30 kg/m^2 was associated with a 79% increase in SCD risk after adjustment for age, sex, smoking, blood pressure, diabetes, cholesterol, baseline cardiac disease, and ECG abnormalities.[24] Data from the Paris Prospective Study and the Nurses' Health Study also demonstrated that obesity is an independent risk factor for SCD, but, interestingly, not for fatal MI/CAD.[28,45,46] Moreover, data from the Paris Prospective Study[26] showed that abdominal obesity increases the risk of SCD regardless of BMI, and the association was stronger between abdominal obesity and SCD than between abdominal obesity and fatal MI (**Figure 2**).

These findings indicate that obesity, and especially visceral obesity, may also increase the risk of SCD independent of CAD. A study of 2,185 middle-aged men reported somewhat contradictory findings, suggesting that metabolically healthy overweight/obese are not at an increased risk of SCD.[47] However, this study of a relatively small, poorly powered sample combined overweight (BMI 25-30 kg/m^2) and obese individuals. Larger meta-analyses have reported that metabolically healthy obese individuals are at an increased risk for cardiovascular events and overall mortality.[48,49] Metabolically healthy obesity may represent a "honeymoon phase" of obesity, with the majority of individuals developing metabolic abnormalities during follow-up.[40,41]

PHYSICAL ACTIVITY AND SCD. In addition to metabolic abnormalities, low exercise capacity may also confound increased SCD risk in obesity. Low exercise capacity predicts SCD,[50] and data from a cohort of 2,357 middle-aged men suggested that high BMI was not associated with SCD after adjustment for peak oxygen uptake.[51] The interaction between BMI and exercise capacity is also likely to be complex because high BMI in physically active individuals may result from increased muscle mass instead of adipose tissue. Measures of visceral obesity (eg, waist circumference, WHR, SAD) would probably provide more accurate

estimations of the interaction between physical activity and obesity-related SCD risk. The direct exercise capacity test provides an accurate estimation of fitness, but it does not quantify the amount of weekly physical activity that could attenuate the excess of obesity-related cardiovascular risk. Of note, a study of 116,564 women found that high physical activity (>3.5 hours of exercise per week) did not eliminate the increased risk of overall death from obesity.[52] Further studies are needed to evaluate the interaction between cardiorespiratory fitness, weekly physical activity, abdominal obesity, and SCD risk in more detail.

CLINICAL CHARACTERISTICS AND AUTOPSY FINDINGS

PREVALENCE OF OBESITY IN SCD COHORT STUDIES. Several autopsy series and community-based SCD cohorts have reported that younger SCD victims have a high prevalence of comorbid obesity.[53-58] In the Oregon SUDS (Oregon Sudden Unexpected Death Study), the prevalence of obesity was 24% in SCD cases aged <25 years, and as much as 50% in SCD cases aged 25 to 34 years.[54] Similarly, an SCD registry from Australia showed that 55% of cases aged 18 to 50 years were obese[56]; significantly higher in comparison to the age-matched general population (29%; $P < 0.001$) and associated with high frequency of conventional cardiovascular risk factors. In the Fingesture study, 40% of SCD cases aged <40 years were obese,[57] but somewhat lower estimates were reported from a nation-based cause-of-death registry in Sweden and a referral SCD cohort in the United Kingdom, which has a 15% to 20% prevalence of obesity among SCD cases aged <35 years.[53-58] The prevalence of comorbid obesity may be highest among young and middle-aged SCD cases. In Oregon SUDS, middle-aged SCD cases (35-60 years) were more likely to have obesity in comparison to older SCD cases (48% vs 33%; $P < 0.001$).[59]

AUTOPSY FINDINGS IN OBESE SCD CASES. In addition to accelerated atherosclerosis and CAD development, obesity leads to significant hemodynamic changes (eg, higher blood volume) that promote cardiac hypertrophy, dilatation, HF, and VAs (**Figure 3**).[60-63] Studies on autopsy findings in obesity-related SCD have mainly focused on young individuals, and there is a lack of comprehensive autopsy reports on middle-aged and older obese SCD cases.

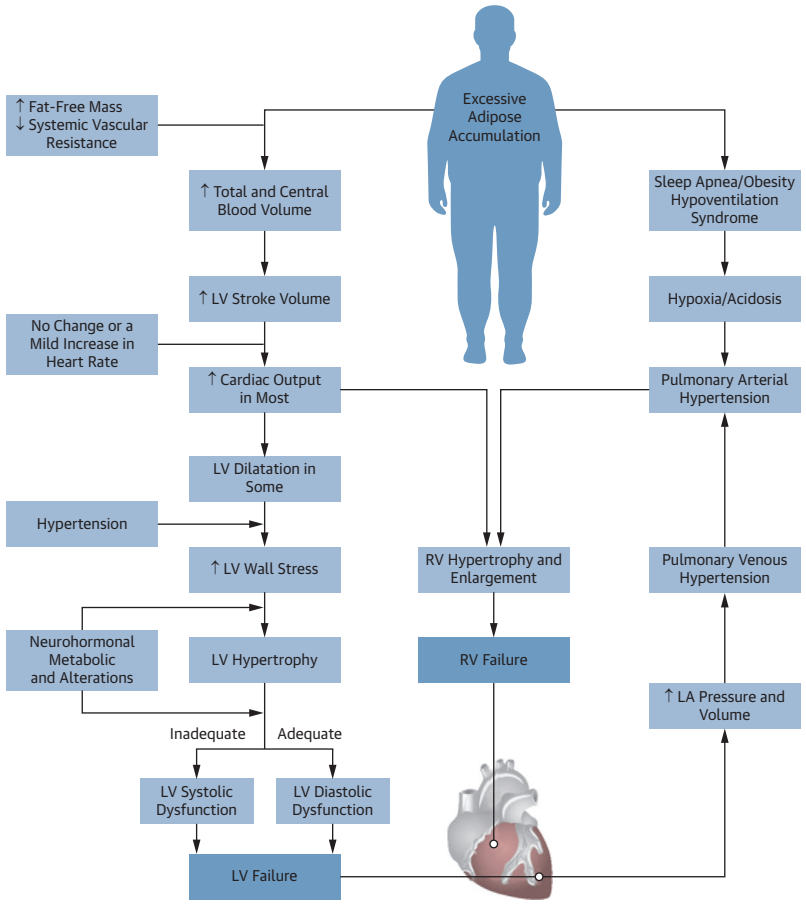
Current evidence indicates that the most common autopsy findings among obese SCD cases are cardiac hypertrophy and CAD when all age groups are included.[56,64-67] Although obesity-related SCD often accompanies cardiac hypertrophy and dilatation, there has been some debate on whether obesity cardiomyopathy is a distinct entity, or whether cardiac remodeling in obesity is rather owing to multiple comorbidities and metabolic alterations. In the Fingesture study, obesity-related hypertrophic cardiac disease (defined as cardiac hypertrophy, chamber dilatation, and excessive epicardial fat in individuals with BMI >30 kg/m^2 in the absence of other explainable causes) was the most common nonischemic autopsy finding among SCDs of all age groups.[60-65] Moreover, autopsy studies of SCD cases from the United Kingdom and the United States also demonstrated that cardiomegaly is a common finding in obesity-related SCD even without concomitant CAD (**Figure 4**).[67,68]

Whereas middle-aged and older SCD cases are often associated with structural cardiac abnormalities, young obese SCD cases may also present with structurally normal hearts at autopsy. However, the proportion of structurally normal hearts among obese SCD victims is smaller than among their leaner counterparts.[53,54,56,69] In addition to cardiac hypertrophy, excessive epicardial fat is associated with an increased risk of VAs in obesity (**Figure 5**).[70] The role of myocardial fat infiltration in arrhythmogenesis and obesity-related SCD is less well studied, but a small autopsy series of young obese SCD victims (n = 7) found that fat infiltration throughout the conduction system was present in 43%, and this finding was pronounced in markedly obese cases.[71]

DIURNAL VARIATION AND PRESENTING RHYTHM IN OBESITY-RELATED SCD. Obesity-related SCD is probably more likely to occur during nighttime hours than SCD in nonobese cases.[72] This phenomenon could potentially be explained by a higher prevalence of obstructive sleep apnea (OSA) in obese individuals. In a cohort of 10,701 adults with polysomnograms followed for an average of 5.3 years, OSA was an independent predictor of SCD, and the magnitude of risk was dependent on the OSA severity, especially nocturnal O_2 saturation.[73] Previous studies have also demonstrated that OSA increases especially the risk of nighttime SCD[74] and that continuous positive airway pressure (CPAP) management decreases the VA burden (**Figure 6**).[75]

OSA may increase the risk of arrhythmia and SCD through multiple mechanisms. Apnea may function as an SCD trigger by inducing parasympathetic activation and bradyarrhythmias with a higher likelihood of nonshockable SCD.[76] Prior studies have also shown that nonshockable SCD is more likely to occur during

FIGURE 3 **Potential Development of Obesity Cardiomyopathy**



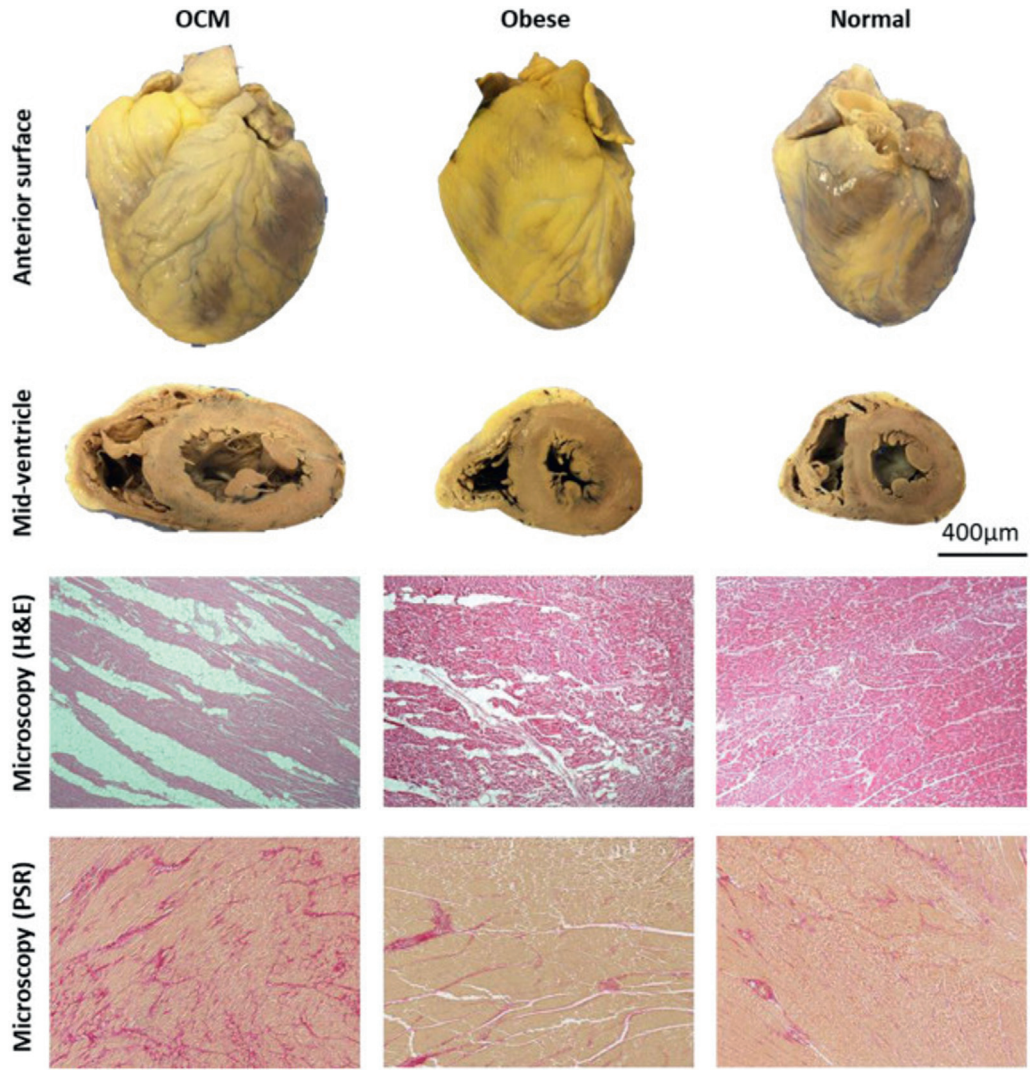
Obesity leads to significant hemodynamic changes (eg, higher blood volume) that promote cardiac hypertrophy, dilatation, and heart failure. LA = left atrium; LV = left ventricle; RV = right ventricle. Reproduced with permission from Lavie et al.[149]

nighttime hours than shockable SCD.[77,78] On the other hand, hypoxemia increases sympathetic activation when apnea terminates, which may in turn increase heart rate and blood pressure. This could trigger VAs due to coronary ischemia, especially in the presence of CAD.[79] The prevalence of previously diagnosed OSA was not higher in nighttime SCD in Oregon SUDS,[72] but this finding may be confounded by the underdiagnosis of OSA.

The existing literature also suggests that obesity may have a stronger association with nonshockable rhythms. A large cardiac arrest registry from Sweden demonstrated that the proportion of shockable rhythm was lower in obese subjects.[32] We have also recently developed an artificial intelligence model to distinguish SCD cases presenting either ventricular fibrillation or pulseless electrical activity.[80] This model identified high weight as a predictor of SCD presenting as pulseless electrical activity, further supporting the association between obesity and nonshockable SCD.

ELECTROCARDIOGRAPHIC ABNORMALITIES IN OBESE SCD VICTIMS. There has been significant interest in identifying SCD risk markers from the 12-lead ECG in anticipation of improving long-term risk stratification.[81-83] Several depolarization and repolarization abnormalities have been associated with an increased risk of SCD in the general population, but the electrocardiographic signal is deteriorated by subcutaneous fat, which may complicate the application of ECG-based risk scores in obese patients.[24]

FIGURE 4 **Obesity and Cardiomegaly**



A study from the United Kingdom reported autopsy findings in sudden cardiac death victims with unexplained cardiomegaly in obesity (OCM) vs control subjects with obesity and normal weight control subjects. Cases with OCM presented with left ventricular enlargement and excess epicardial fat. H&E = hematoxylin and eosin; PSR = picrosirius red stain. Reproduced with permission from Westaby et al.[68]

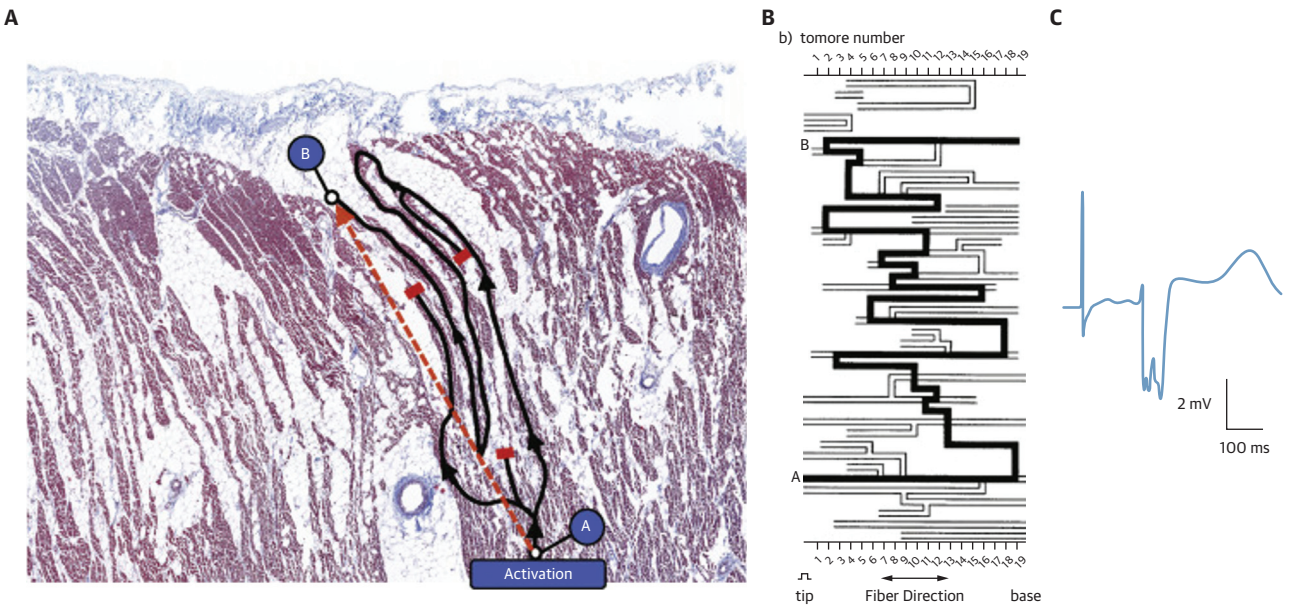
Accordingly, obese individuals have reduced sensitivity for ECG-based left ventricular hypertrophy, prolonged QTc interval, and leftward axis shifts.[84]

There is a shortage of studies investigating SCD risk markers from the resting ECG in obese individuals. Data from Oregon SUDS showed that obese/overweight SCD cases had a significantly higher prevalence of QRS fragmentation in comparison to control subjects.[85] A fragmented QRS complex may be a surrogate marker of conduction disturbances and delayed activation in the myocardium, which is again potentially a result of myocardial fibrosis or fat infiltration.[86] Given the special considerations required for the analysis of ECGs in obese individuals, there is a need for a renewed focus on studies of ECG-based SCD risk markers in obesity.

POTENTIAL MECHANISMS OF LETHAL ARRHYTHMIAS IN OBESITY

The specific pathways leading to lethal arrhythmias in obesity are not fully clear, but obesity is associated

FIGURE 5 Epicardial Adipose Tissue and VAs



(A) Infiltration of adipose tissue in the myocardium and a zigzag electrical activation pattern leading to re-entry are shown. (B) Illustration shows how regional conduction disturbances lengthen the distance and prolong the activation time and (C) illustrates electrogram fractionation due to conduction disturbances. VA = ventricular arrhythmia. Reproduced with permission from Ernault et al.[70] Original data from Vigmond et al[150] and de Bakker et al.[151]

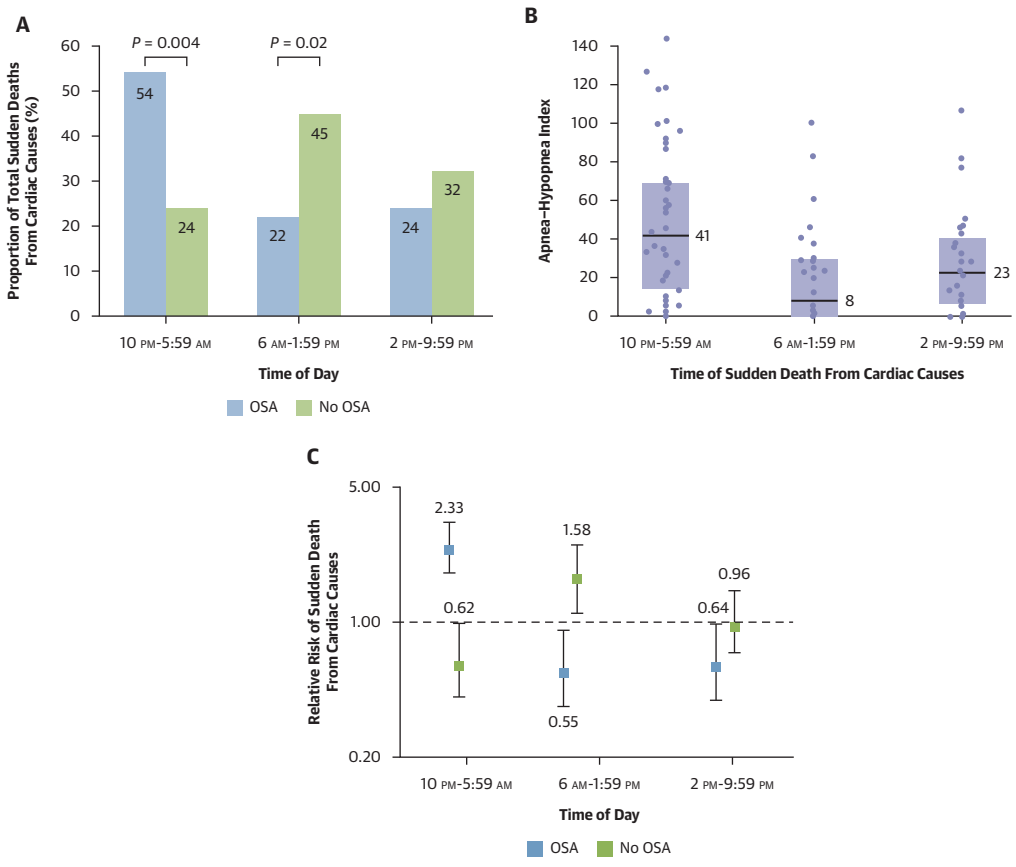
with several pathological alterations in cardiac structure and function that increase the risk of VAs and SCD. These changes can be classified as electrical and structural remodeling of the heart, and because of the common underlying etiologies, the 2 may often coexist.

ELECTRICAL REMODELING. Obese patients present with prolonged QTc interval, which has been associated with an increased risk of SCD in the general population.[87,88] For example, in Oregon SUDS, prolonged QTc was associated with a 5-fold risk of SCD.[89,90] VAs in acquired and inherited long QTc syndromes are thought to be precipitated by early afterdepolarizations, which are secondary voltage depolarizations during the repolarizing phase of the action potential. However, the effect of prolonged QTc on SCD risk may also be explained by prolonged depolarization. Recent data on large general population cohorts suggested that when the QTc interval is deconstructed into depolarization (QRS) and repolarization (JTc) intervals, the repolarization component may have no or only little independent prognostic value for SCD.[91]

In obesity, increased adipose tissue leads to abnormally high expression of the aromatase enzyme, which converts testosterone to estrogens. Whereas testosterone shortens the action potential, estrogens prolong the QTc interval by reducing the myocardial potassium channel current. The effect of adipose tissue on QTc lengthening is also supported by prior studies that have shown that QTc duration shortens significantly in response to weight loss after bariatric surgery.[92] In addition to prolonged QRS and QTc intervals, other possible electrical triggers for arrhythmogenicity in obesity are abnormal upregulation of the sympathetic nervous system, increased heart rate, and decreased heart rate variability.[93]

STRUCTURAL REMODELING. Obesity is often accompanied by cardiac hypertrophy and dilatation, which are also common findings in postmortem investigations of SCD. Increased heart weight develops in parallel with increased body size, and current guidelines recommend indexing cardiac chamber measurements to body surface area to allow comparison among patients with different body sizes.[94] However, structural remodeling in response to increased body size may not be benign, and an absolute increase in cardiac hypertrophy has been associated with an approximately 3-fold increased

FIGURE 6 OSA and Diurnal Variation of Sudden Death



A study on polysomnograms and the death certificates of 112 sudden cardiac death victims found that cases with obstructive sleep apnea (OSA) had a peak in sudden cardiac death occurrence during sleeping hours. Reproduced with permission from Gami et al.[74]

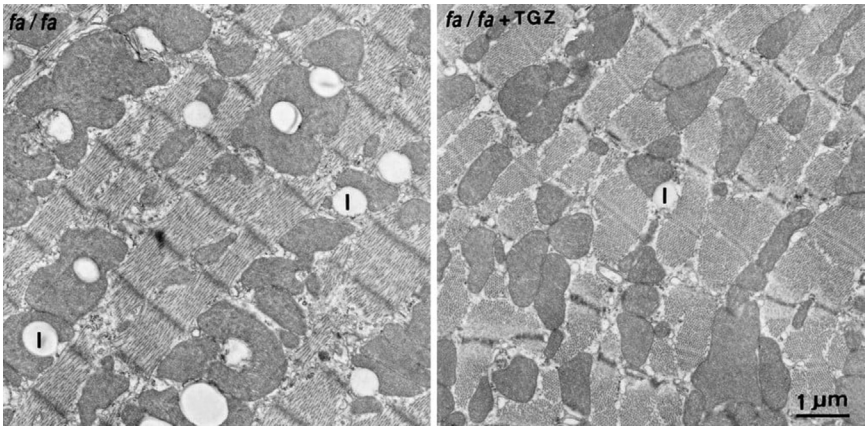
risk of SCD.[95-97] This excess risk is independent of, and additive to, the risk conferred by severely reduced left ventricular ejection fraction.[98]

The pathophysiological mechanisms of how cardiac hypertrophy increases the risk of SCD are likely multifactorial, but ischemia and myocardial fibrosis are probably the most important. Ischemia due to cardiac hypertrophy may arise from insufficient compensatory coronary artery growth and failure of coronary artery dilatation due to increased ventricular tension and stiffness.[99] Cardiac hypertrophy is also often associated with myocardial fibrosis,[100,101] which increases the distance between adjacent myocytes and disturbs physiological electrical propagation, eventually leading to anatomic re-entry.[102] In a cardiac magnetic resonance imaging study, the association between myocardial fibrosis and SCD was stronger than the association between left ventricular ejection fraction and SCD.[103]

FATTY HEART. The concept of the fatty heart has been described in the medical literature for at least 200 years,[104,105] and has since been vigorously debated. Recognition of the global obesity epidemic at the end of the 20th century focused significantly on the possible existence of obesity-related cardiomyopathy.[106]

In the early 2000s, Zhou et al[107] demonstrated that obese rats developed lipid droplets in the myocardium and that cardiac dysfunction in such rats was caused by cardiac lipoapoptosis (**Figure 7**). Subsequently, intramyocardial lipid accumulation was found in nonischemic human HF, with the highest tissue levels among patients with diabetes

FIGURE 7 Intramyocardial Lipid Accumulation



Lipid droplets in myocardium sections of an untreated obese Zucker Diabetic Fatty (ZDF) rat (fa/fa) (left) and a troglitazone-treated obese ZDF rat (fa/fa + TGZ) (right). Lipid droplets appear in white and are marked with an I. fa = fatty acid. Reproduced with permission from Zhou et al.[107]

and obesity.[108] The development of "lipotoxic cardiomyopathy" is thought to occur because of a mismatch between cardiomyocyte fatty acid intake and oxidation. Fatty acids are a key source of energy for cardiomyocytes, and increased levels of circulating free fatty acids in obesity may lead to a disproportionally high level of fatty acid intake in the heart, which exceeds the mitochondrial oxidative capacity and leads to organ dysfunction.[106]

In addition to lipid accumulation in cardiomyocytes, prior studies have found that adipose tissue can accumulate in infarcted myocardium and colocalize with fibrosis.[109,110] Similarly to myocardial fibrosis, fat infiltration in the myocardium disturbs physiological electrical propagation and predisposes to VAs.[111] Given the colocalization with myocardial scars, 1 potential mechanism is fatty degeneration following MI. Fatty replacement of the myocardium is also a hallmark of arrhythmogenic right ventricular cardiomyopathy that is also associated with increased risk of SCD.[112] However, the potential role of myocardial lipid accumulation and fatty replacement in the broader group of SCD victims is yet to be proven. Moreover, it is unclear whether the accumulation of intramyocardial fat after MI is related to obesity.

CLINICAL IMPLICATIONS

Sudden cardiac arrest is an extremely lethal event and leads to death within 10 minutes if life-supporting interventions are not rapidly initiated. Although acute management of out-of-hospital cardiac arrests has improved in recent decades, long-term prediction and prevention remain the cornerstones of successful reduction of the premature SCD burden. Lifestyle intervention, weight-reducing diets, and exercise advice are likely to reduce premature all-cause mortality,[113] and recent progress in obesity management (novel pharmacotherapies and bariatric surgery) has shown promising results in weight loss and reducing clinical risk factors.

CLINICAL BENEFITS OF GLP-1 AGONISTS AND BARIATRIC SURGERY. In 2014, the U.S. Food and Drug Administration approved the first glucagon-like peptide-1 (GLP-1) agonist to treat obesity, and since then, a growing body of evidence has demonstrated the cardiovascular benefits of GLP-1 agonists. In the STEP-1 (Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity) randomized trial, overweight and obese patients receiving GLP-1 agonist semaglutide achieved a mean body weight loss of 14.9%, which was significantly better in comparison to placebo (2.4%) and accompanied by a greater reduction in clinical risk factors.[114] The effect of GLP-1 agonists on cardiovascular outcomes was first tested in patients with diabetes, and several trials have demonstrated significant reductions in cardiovascular death (~13%), nonfatal MI (~9%), and HF hospitalization (~9%).[115] Beneficial effects on obesity led to a hypothesis that GLP-1 agonists may reduce outcomes in nondiabetic obese patients as well. Recently published SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity)

trial found that GLP-1 agonist semaglutide reduces major cardiovascular events (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) also in nondiabetic obese patients with preexisting cardiovascular disease by ~20%.[116]

Weight reduction by GLP-1 agonists is mediated via the stimulation of satiety and reduction of food intake.[117] A recent meta-analysis demonstrated that GLP-1 treatment leads to a decrease in both visceral and subcutaneous adipose tissue, and visceral adipose tissue reduction may be greater than subcutaneous adipose tissue reduction.[118] GLP-1 receptors are also expressed in the heart and blood vessels, and hence might have direct effects on the cardiovascular system independent of weight reduction.[117] There is, as yet, no robust evidence of the effect of weight loss or GLP-1 agonists on SCD risk. However, these recent developments are promising and future investigations are needed to examine whether GLP-1 agonists could reduce the burden of premature SCD in obese patients.

Surgical interventions for obesity have been reported since the second half of the 20th century. After the first laparoscopic gastric bypass was performed in 1994, there was rapid growth in the number of bariatric surgeries performed.[119] Bariatric surgery is associated with greater weight reduction in comparison to pharmacological therapy (20%-30%), but the risks of surgery remain higher.[114,120] Bariatric surgery has also been shown to associate with reduced cardiovascular risk factors and lower premature cardiovascular mortality,[120,121] but any effect on SCD risk has not been reported.

SCD RISK STRATIFICATION AND PREVENTION IN OBESITY. Long-term prediction and prevention of SCD are currently based on the assessment of left ventricular ejection fraction and the implantation of ICD for high-risk patients.[122] Whereas the primary prevention ICD remains important, the approach to risk stratification likely needs to be revisited. Of note, advances in HF management have led to an approximately 44% decline in the rate of SCD in HF[123] with a concomitant reduction in ICD therapy events.[124,125] Accurate SCD risk stratification in obesity is likely to require a combination of various biomarkers, including, for example, metabolic alterations, -omics data, cardiovascular imaging, and ECG, as well as more sophisticated measurements of body composition and fat distribution than anthropometric measures (eg, dual-energy x-ray absorptiometry).

Reducing the burden of SCD in obesity will require a comprehensive approach. Obesity is a result of a chronic mismatch between energy intake and consumption, and the underlying reasons for high energy intake are multifactorial including behavioral, genetic, and environmental determinants. The rapid increase in obesity in the last decades is not explainable by genetic or physiological changes, and according to previous studies, the most important causes for the increase in obesity are due to environmental changes that enable high energy intake (eg, large portion sizes, the high-energy density of the foods).[126,127] Although weight loss and bariatric surgery lead to clinical benefits in various cardiovascular diseases[128], clinical guidance and the development of the health care system alone are likely not enough to curb the obesity epidemic, and more extensive consideration at the broader societal as well as health-policy levels will also be required.[129]

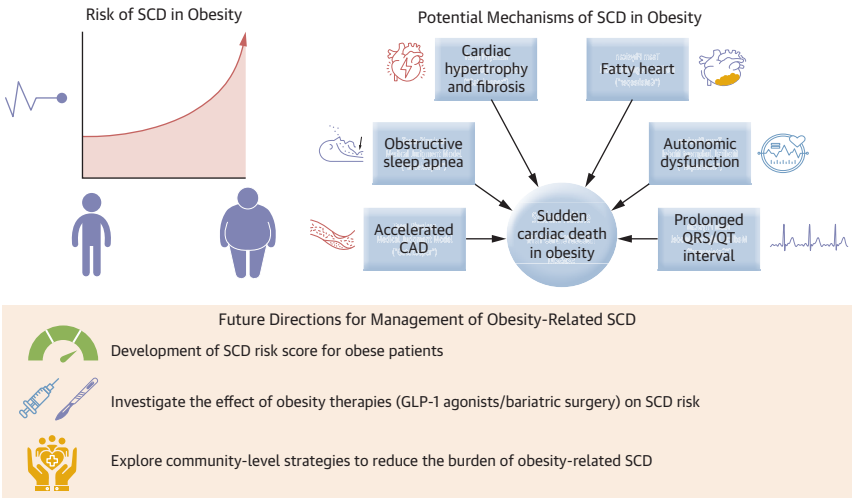
KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Published studies have demonstrated that increased BMI and especially visceral obesity carry an increased risk of SCD. Even though the available literature provides valuable insights into obesity-related SCD, several knowledge gaps remain (**Central Illustration**).

Current evidence suggests that the increased SCD risk in obesity is not fully explainable by traditional cardiovascular risk factors and accelerated development of CAD/MI. All mediators for SCD risk in obesity are not fully understood, and other potential mediators include, for example, elevated free fatty acids,[130-132] genetics,[133] and obesity cardiomyopathy. Intramyocardial fat can be detected with contrast-enhanced computed tomography,[134,135] and prior studies have shown that accumulation of fat in the myocardium leads to conduction disturbances and may predispose to VAs.[111] However, prior studies have focused on post-MI patients, and it remains unclear whether intramyocardial fat is related to SCD in obese patients without CAD, or whether obesity is related to the amount of intramyocardial fat. A better understanding of SCD mediators in obesity is crucial for improving long-term prediction and prevention as well as identifying potential therapeutic targets. Further research is needed to investigate potential SCD mechanisms beyond CAD and traditional risk factors.

The traditional definition of obesity is based on the measurement of BMI, but current evidence suggests that measures of visceral obesity are better predictors of morbidity and mortality.[12] Indicators that are more precise than BMI warrant further investigation to enhance the identification and prevention of cardiovascular disease risk. Emerging metrics, such as body fat distribution or body composition may provide a

CENTRAL ILLUSTRATION **Sudden Cardiac Death in Obesity: Potential Mechanisms and Future Directions for Management**


Risk of SCD in Obesity
Potential Mechanisms of SCD in Obesity
Cardiac hypertrophy and fibrosis
Fatty heart
Obstructive sleep apnea
Autonomic dysfunction
Accelerated CAD
Sudden cardiac death in obesity
Prolonged QRS/QT interval
Future Directions for Management of Obesity-Related SCD
Development of SCD risk score for obese patients
Investigate the effect of obesity therapies (GLP-1 agonists/bariatric surgery) on SCD risk
Explore community-level strategies to reduce the burden of obesity-related SCD

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Visceral obesity increases the risk of sudden cardiac death (SCD), which is likely mediated by several alterations in the cardiovascular system due to obesity. Future studies are required to investigate novel individual and community-based methods to decrease the burden of obesity-related SCD. CAD = coronary artery disease; GLP-1 = glucagon-like peptide-1.

more accurate assessment of obesity than traditional anthropometric measures and should be assessed in future studies.

Further efforts are also needed to investigate the effect of novel obesity therapies on SCD risk. The SELECT trial demonstrated that GLP-1 agonists reduce the risk of major cardiovascular events, but the effect on SCD burden remains unknown. GLP-1 agonists have been associated with increased resting heart rate (a risk factor for SCD), which has raised some safety concerns regarding the risk of VAs.[136] In patients with type 2 diabetes, GLP-1 agonists have not been shown to increase or decrease the risk of VAs or SCD,[137,138] but the effects in patients with obesity need detailed investigation. With current medical therapy, the event rate of SCD could be lower in the general population, which challenges the detection of statistically and clinically meaningful effects. Feasible studies will require a large sample size and a careful selection of patients with obesity and a high risk of SCD. The development of an accurate SCD risk stratification in obesity may be a prerequisite for studying the effectiveness of GLP-1 agonists in reducing the risk of obesity-related SCD.

Current guidelines recommend preventive ICD therapy only for those with ejection fraction ≤35% (primary prevention) or a history of a life-threatening arrhythmia (secondary prevention).[122] A major limitation of the current approach to primary prevention is low sensitivity, because at least 70% of SCD cases occur in subjects that are not classified as high-risk patients and do not fulfill the current criteria for ICD implantation.[139] Approximately 40% to 50% of SCDs may even be the first manifestation of the underlying cardiac disease,[1] and low-cost high-throughput screening tools, especially ECG, should be of interest. Accumulation of ECG abnormalities into electrical risk scores has been shown to have a relatively good ability to identify patients at high risk of SCD,[81,82] and ECG abnormalities can also improve risk prediction when added to clinical risk markers.[140] However, the usefulness of ECG risk scores may be affected by body fat,[24] and the development of body fat-adjusted ECG risk scores is probably warranted to improve ECG-based screening methods in obese patients. Most recently, an artificial intelligence algorithm that can predict SCD risk from the entire waveform instead of individual ECG risk markers has been made available.[141]

The development of SCD is generally thought to require a combination of an underlying cardiac substrate with 1 or more triggers. Whereas obesity-

related cardiac hypertrophy and CAD can create a substrate for SCD, obstructive sleep apnea may act as a potential trigger for life-threatening arrhythmias. Epidemiological evidence supports the role of obstructive sleep apnea as an SCD precipitator,[73,74,79] but previous randomized trials of CPAP for secondary cardiovascular prevention in obstructive sleep apnea have reported neutral findings.[142-144] However, these randomized trials have been criticized due to the exclusion of high-risk patients and low adherence to CPAP therapy, and the effect of CPAP therapy on reducing SCD risk in obese patients remains inconclusive.

The association between obesity and SCA presentation with higher rates of nonshockable rhythms could result in worse survival outcomes and needs further investigation. For example, are the higher rates of pulseless electrical activity and asystole in obese individuals directly related to the "obesity substrate," or confounded by SCA circumstances and resuscitation-related factors in obese individuals? If SCA survival is lower in obese individuals, how could outcomes be improved?

The impact of obesity on SCD across socioeconomic status and racial/ethnic groups needs further investigation. There are significant differences in the prevalence of obesity with regard to race/ethnicity and social determinants. For example, obesity is more common among some U.S. racial/ethnic minorities, such as African Americans and Hispanic Americans, as well as in lower socioeconomic groups, but the prevalence is lower in Asian Americans.[145,146] Consistently, the risk of SCD is higher among African Americans and in lower socioeconomic groups,[3,147] but it is unclear to what extent this is explained by the higher rates of obesity. Obesity may hence have a higher impact on the overall SCD burden in some communities. A recent multiethnic community-based study from the United States found that whereas the SCD rate was similar in Hispanic and White individuals, obesity and lower socioeconomic status were more commonly observed as risk factors among Hispanic individuals.[148] Socioeconomic disadvantages and variable access to preventive health care may have an important effect on the risk of obesity and SCD, and targeted community-specific education and preventive health care have the potential to improve early diagnosis and SCD prevention. More work is needed to investigate the burden and characteristics of obesity-related SCD across diverse communities.

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REFERENCES

1. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med*. 2001;345(20):1473–1482.

2. Lynge TH, Risgaard B, Banner J, et al. Nationwide burden of sudden cardiac death: a study of 54,028 deaths in Denmark. *Heart Rhythm*. 2021;18(10):1657–1665.

3. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153–e639.

4. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2010;3(1):63–81.

5. Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis*. 2008;51(3):213–228.

6. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98(21):2334–2351.

7. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol*. 2004;44(6):1268–1275.

8. Haukilahti MAE, Holmstrom L, Vahatalo J, et al. Sudden cardiac death in women. *Circulation*. 2019;139(8):1012–1021.

9. Holmstrom L, Juntunen S, Vahatalo J, et al. Plaque histology and myocardial disease in sudden coronary death: the Fingesture study. *Eur Heart J*. 2022;43(47):4923–4930.

10. Gray B, Ackerman MJ, Semsarian C, Behr ER. Evaluation after sudden death in the young: a global approach. *Circ Arrhythm Electrophysiol*. 2019;12(8):e007453.

11. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143(21):e984–e1010.

12. Bigaard J, Frederiksen K, Tjonneland A, et al. Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. *Int J Obes (Lond)*. 2005;29(7):778–784.

13. Adabag S, Huxley RR, Lopez FL, et al. Obesity related risk of sudden cardiac death in the atherosclerosis risk in communities study. *Heart*. 2015;101(3):215–221.

14. National Heart, Lung, and Blood Institute. *Clinical Guidelines on the Identification, Evaluation, Treatment of Overweight and Obesity in Adults. The Evidence Report*. National Institutes of Health; 1998. NIH publication 98-4083.

15. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6(12):944–953.

16. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923–1994.

17. Stierman B, Afful J, Carroll M, et al. National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files—Development of Files and Prevalence Estimates for Selected Health Outcomes. *National Health Statistics Reports*. 2021:158.

18. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27.

19. Aune D, Schlesinger S, Norat T, Riboli E. Body mass index, abdominal fatness, and the risk of sudden cardiac death: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2018;33(8):711–722.

20. Doyle JT, Kannel WB, McNamara PM, Quickenton P, Gordon T. Factors related to suddenness of death from coronary disease: combined Albany-Framingham studies. *Am J Cardiol*. 1976;37(7):1073–1078.

21. Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. *Am J Cardiol*. 1977;39(3):452–458.

22. Younis A, Goldberger JJ, Kutyifa V, et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. *Eur Heart J*. 2021;42(17):1676–1684.

23. Shadman R, Poole JE, Dardas TF, et al. A novel method to predict the proportional risk of sudden cardiac death in heart failure: derivation of the Seattle Proportional Risk Model. *Heart Rhythm*. 2015;12(10):2069–2077.

24. Eranti A, Aro AL, Kerola T, et al. Body mass index as a predictor of sudden cardiac death and usefulness of the electrocardiogram for risk stratification. *Am J Cardiol*. 2016;117(3):388–393.

25. Escobedo LG, Zack MM. Comparison of sudden and nonsudden coronary deaths in the United States. *Circulation*. 1996;93(11):2033–2036.

26. Empana JP, Ducimetiere P, Charles MA, Jouven X. Sagittal abdominal diameter and risk of sudden death in asymptomatic middle-aged men: the Paris Prospective Study I. *Circulation*. 2004;110(18):2781–2785.

27. Bertoia ML, Allison MA, Manson JE, et al. Risk factors for sudden cardiac death in postmenopausal women. *J Am Coll Cardiol*. 2012;60(25):2674–2682.

28. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation*. 2008;117(13):1658–1667.

29. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006;368(9536):666–678.

30. Jahangir A, Mirza M, Shahreyar M, et al. Presence of obesity is associated with lower mortality in elderly patients with implantable cardioverter defibrillator. *Int J Obes (Lond)*. 2018;42(2):169–174.

31. Aoki M, Aso S, Suzuki M, et al, SOS-KANTO 2017 Study Group. Association between obesity and neurological outcomes among out-of-hospital cardiac arrest patients: The SOS-KANTO 2017 study. *Resusc Plus*. 2024;17:100513.

32. Hjalmarsson A, Rawshani A, Ramunddal T, et al. No obesity paradox in out-of-hospital cardiac arrest: data from the Swedish Registry of Cardiopulmonary Resuscitation. *Resusc Plus*. 2023;15:100446.

33. Kakavas S, Georgiopoulos G, Oikonomou D, et al. The impact of body mass index on post resuscitation survival after cardiac arrest: A meta-analysis. *Clin Nutr ESPEN*. 2018;24:47–53.

34. Ma Y, Huang L, Zhang L, Yu H, Liu B. Association between body mass index and clinical outcomes of patients after cardiac arrest and resuscitation: a meta-analysis. *Am J Emerg Med*. 2018;36(7):1270–1279.

35. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9:88.

36. Jung RT. Obesity as a disease. *Br Med Bull*. 1997;53(2):307–321.

37. Lehtovirta M, Pietilainen KH, Levalahti E, et al. Evidence that BMI and type 2 diabetes share only a minor fraction of genetic variance: a follow-up study of 23,585 monozygotic and dizygotic twins from the Finnish Twin Cohort Study. *Diabetologia*. 2010;53(7):1314–1321.

38. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002;162(16):1867–1872.

39. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289(1):76–79.

40. Karajamaki AJ, Korkiakoski A, Hukkanen J, Kesaniemi YA, Ukkola O. Long-term metabolic fate and mortality in obesity without metabolic syndrome. *Ann Med*. 2022;54(1):1432–1443.

41. Lin H, Zhang L, Zheng R, Zheng Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: a PRISMA-compliant article. *Medicine (Baltimore)*. 2017;96(47):e8838.

42. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest*. 2019;129(10):3978–3989.

43. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640–1645.

44. Kurl S, Laaksonen DE, Jae SY, et al. Metabolic syndrome and the risk of sudden cardiac death in middle-aged men. *Int J Cardiol*. 2016;203:792–797.

45. Chiuve SE, Sun Q, Sandhu RK, et al. Adiposity throughout adulthood and risk of sudden cardiac death in women. *J Am Coll Cardiol EP*. 2015;1(6):520–528.

46. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation*. 1999;99(15):1978–1983.

47. Jae SY, Kurl S, Fernhall B, Kunutsor SK, Franklin BA, Laukkanen JA. Are metabolically healthy overweight/obese men at increased risk of sudden cardiac death? *Mayo Clin Proc*. 2018;93(9):1266–1270.

48. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758–769.

49. Zheng R, Zhou D, Zhu Y. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2016;70(10):1024–1031.

50. Laukkanen JA, Makikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study. *J Am Coll Cardiol*. 2010;56(18):1476–1483.

51. Jae SY, Franklin BA, Kurl S, et al. Effect of cardiorespiratory fitness on risk of sudden cardiac death in overweight/obese men aged 42 to 60 years. *Am J Cardiol*. 2018;122(5):775–779.

52. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med*. 2004;351(26):2694–2703.

53. Finocchiaro G, Papadakis M, Dhutia H, et al. Obesity and sudden cardiac death in the young: clinical and pathological insights from a large national registry. *Eur J Prev Cardiol*. 2018;25(4):395–401.

54. Jayaraman R, Reinier K, Nair S, et al. Risk factors of sudden cardiac death in the young: multiple-year community-wide assessment. *Circulation*. 2018;137(15):1561–1570.

55. Krexi D, Sheppard MN. Cardiovascular causes of maternal sudden death. Sudden arrhythmic death syndrome is leading cause in UK. *Eur J Obstet Gynecol Reprod Biol*. 2017;212:155–159.

56. Paratz ED, Ashokkumar S, van Heusden A, et al. Obesity in young sudden cardiac death: rates, clinical features, and insights into people with body mass index >50kg/m^2. *Am J Prev Cardiol*. 2022;11:100369.

57. Vahatalo J, Holmstrom L, Pakanen L, et al. Temporal trends in the incidence and characteristics of sudden cardiac death among subjects under 40 years of age in Northern Finland during 1998-2017. *Cardiology*. 2022;147(3):328–331.

58. Wisten A, Krantz P, Stattin EL. Sudden cardiac death among the young in Sweden from 2000 to 2010: an autopsy-based study. *Europace*. 2017;19(8):1327–1334.

59. Noheria A, Teodorescu C, Uy-Evanado A, et al. Distinctive profile of sudden cardiac arrest in middle-aged vs. older adults: a community-based study. *Int J Cardiol*. 2013;168(4):3495–3499.

60. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev*. 2008;88(2):389–419.

61. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347(5):305–313.

62. Russo C, Jin Z, Homma S, et al. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J Am Coll Cardiol*. 2011;57(12):1368–1374.

63. Messerli FH, Nunez BD, Ventura HO, Snyder DW. Overweight and sudden death. Increased ventricular ectopy in cardiopathy of obesity. *Arch Intern Med*. 1987;147(10):1725–1728.

64. Duflou J, Virmani R, Rabin I, Burke A, Farb A, Smialek J. Sudden death as a result of heart disease in morbid obesity. *Am Heart J*. 1995;130(2):306–313.

65. Hookana E, Junttila MJ, Puurunen VP, et al. Causes of nonischemic sudden cardiac death in the current era. *Heart Rhythm*. 2011;8(10):1570–1575.

66. Kortelainen ML, Porvari K. Extreme obesity and associated cardiovascular disease verified at autopsy: time trends over 3 decades. *Am J Forensic Med Pathol*. 2011;32(4):372–377.

67. Tavora F, Zhang Y, Zhang M, et al. Cardiomegaly is a common arrhythmogenic substrate in adult sudden cardiac deaths, and is associated with obesity. *Pathology*. 2012;44(3):187–191.

68. Westaby J, Dalle-Carbonare C, Ster IC, Sheppard MN. Obesity cardiomyopathy in sudden cardiac death. *JACC Adv*. 2023;2(5):100414.

69. Ha FJ, Han HC, Sanders P, et al. Sudden cardiac death in the young: incidence, trends, and risk factors in a nationwide study. *Circ Cardiovasc Qual Outcomes*. 2020;13(10):e006470.

70. Ernault AC, Meijborg VMF, Coronel R. Modulation of cardiac arrhythmogenesis by epicardial adipose tissue: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78(17):1730–1745.

71. Bharati S, Lev M. Cardiac conduction system involvement in sudden death of obese young people. *Am Heart J*. 1995;129(2):273–281.

72. Ramireddy A, Chugh HS, Reinier K, et al. Sudden cardiac death during nighttime hours. *Heart Rhythm*. 2021;18(5):778–784.

73. Gami AS, Olson EJ, Shen WK, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. *J Am Coll Cardiol*. 2013;62:610–616.

74. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352(12):1206–1214.

75. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. *Thorax*. 2005;60(9):781–785.

76. Holmstrom L, Salmasi S, Chugh H, et al. Survivors of sudden cardiac arrest presenting with pulseless electrical activity: clinical substrate, triggers, long-term prognosis. *J Am Coll Cardiol EP*. 2022;8(10):1260–1270.

77. Bagai A, McNally BF, Al-Khatib SM, et al. Temporal differences in out-of-hospital cardiac arrest incidence and survival. *Circulation*. 2013;128(24):2595–2602.

78. Karlsson LI, Wissenberg M, Fosbol EL, et al. Diurnal variations in incidence and outcome of out-of-hospital cardiac arrest including prior comorbidity and pharmacotherapy: a nationwide study in Denmark. *Resuscitation*. 2014;85:1161–1168.

79. Mehra R, Chung MK, Olshansky B, et al. Sleep-disordered breathing and cardiac arrhythmias in adults: mechanistic insights and clinical implications: a scientific statement from the American Heart Association. *Circulation*. 2022;146(9):e119–e136.

80. Holmstrom L, Bednarski B, Chugh H, et al. Artificial intelligence model predicts sudden cardiac arrest manifesting with pulseless electric activity versus ventricular fibrillation. *Circ Arrhythm Electrophysiol*. 2024;17(2):e012338.

81. Aro AL, Reinier K, Rusinaru C, et al. Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. *Eur Heart J*. 2017;38(40):3017–3025.

82. Chatterjee NA, Tikkanen JT, Panicker GK, et al, PREDETERMINE Investigators. Simple electrocardiographic measures improve sudden arrhythmic death prediction in coronary disease. *Eur Heart J*. 2020;41(21):1988–1999.

83. Holkeri A, Eranti A, Haukilahti MAE, et al. Predicting sudden cardiac death in a general population using an electrocardiographic risk score. *Heart*. 2020;106(6):427–433.

84. Fraley MA, Birchem JA, Senkottaiyan N, Alpert MA. Obesity and the electrocardiogram. *Obes Rev*. 2005;6:275–281.

85. Narayanan K, Zhang L, Kim C, et al. QRS fragmentation and sudden cardiac death in the obese and overweight. *J Am Heart Assoc*. 2015;4(3):e001654.

86. Das MK, Saha C, El Masry H, et al. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. *Heart Rhythm*. 2007;4(11):1385–1392.

87. el-Gamal A, Gallagher D, Nawras A, et al. Effects of obesity on QT, RR, and QTc intervals. *Am J Cardiol*. 1995;75(14):956–959.

88. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47(2):362–367.

89. Chugh SS, Reinier K, Singh T, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. *Circulation*. 2009;119(5):663–670.

90. Teodorescu C, Reinier K, Uy-Evanado A, et al. Prolonged QRS duration on the resting ECG is associated with sudden death risk in coronary disease, independent of prolonged ventricular repolarization. *Heart Rhythm*. 2011;8(10):1562–1567.

91. Tikkanen JT, Kentta T, Porthan K, et al. Risk of sudden cardiac death associated with QRS, QTc, and JTc intervals in the general population. *Heart Rhythm*. 2022;19(8):1297–1303.

92. Al-Salameh A, Allain J, Jacques A, Verhaeghe P, Desailloud R. Shortening of the QT interval is observed soon after sleeve gastrectomy in morbidly obese patients. *Obes Surg*. 2014;24(1):167–170.

93. Mehra R, Tjurmina OA, Ajijola OA, et al. Research opportunities in autonomic neural mechanisms of cardiopulmonary regulation: a report from the National Heart, Lung, and Blood Institute and the National Institutes of Health Office of the Director Workshop. *J Am Coll Cardiol Basic Trans Science*. 2022;7(3):265–293.

94. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233–270.

95. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol*. 1998;32(5):1454–1459.

96. Kaikkonen KS, Kortelainen ML, Huikuri HV. Comparison of risk profiles between survivors and victims of sudden cardiac death from an acute coronary event. *Ann Med*. 2009;41(2):120–127.

97. Chugh SS, Reinier K, Uy-Evanado A, et al. Prediction of sudden cardiac death manifesting with documented ventricular fibrillation or pulseless ventricular tachycardia. *J Am Coll Cardiol EP*. 2022;8(4):411–423.

98. Reinier K, Dervan C, Singh T, et al. Increased left ventricular mass and decreased left ventricular systolic function have independent pathways

to ventricular arrhythmogenesis in coronary artery disease. *Heart Rhythm*. 2011;8(8):1177–1182.

99. Harrison DG, Marcus ML, Dellsperger KC, Lamping KG, Tomanek RJ. Pathophysiology of myocardial perfusion in hypertension. *Circulation*. 1991;83(suppl 5):III14–III18.

100. Holmstrom L, Haukilahti A, Vahatalo J, et al. Electrocardiographic associations with myocardial fibrosis among sudden cardiac death victims. *Heart*. 2020;106(13):1001–1006.

101. Tamarappoo BK, John BT, Reinier K, et al. Vulnerable myocardial interstitium in patients with isolated left ventricular hypertrophy and sudden cardiac death: a postmortem histological evaluation. *J Am Heart Assoc*. 2012;1(3):e001511.

102. de Jong S, van Veen TA, van Rijen HV, de Bakker JM. Fibrosis and cardiac arrhythmias. *J Cardiovasc Pharmacol*. 2011;57(6):630–638.

103. Zegard A, Okafor O, de Bono J, et al. Myocardial fibrosis as a predictor of sudden death in patients with coronary artery disease. *J Am Coll Cardiol*. 2021;77(1):29–41.

104. Corvisart JN. *Of the Degeneration of the Muscular Tissue of the Heart Into Fat. An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels*. Bradford & Read; 1812.

105. Hosmer A. Two cases in which sudden death was caused by fatty degeneration of the heart. *Boston Med Surg J*. 1864;70:319–321.

106. Szczepaniak LS, Victor RG, Orci L, Unger RH. Forgotten but not gone: the rediscovery of fatty heart, the most common unrecognized disease in America. *Circ Res*. 2007;101(8):759–767.

107. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*. 2000;97(4):1784–1789.

108. Sharma S, Adrogue JV, Golfman L, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J*. 2004;18(14):1692–1700.

109. Baroldi G, Silver MD, De Maria R, Parodi O, Pellegrini A. Lipomatous metaplasia in left ventricular scar. *Can J Cardiol*. 1997;13(1):65–71.

110. Su L, Siegel JE, Fishbein MC. Adipose tissue in myocardial infarction. *Cardiovasc Pathol*. 2004;13(2):98–102.

111. Sung E, Prakosa A, Zhou S, et al. Fat infiltration in the infarcted heart as a paradigm for ventricular arrhythmias. *Nat Cardiovasc Res*. 2022;1(10):933–945.

112. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. 2019;16(11):e301–e372.

113. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849.

114. Wilding JPH, Batterham RL, Calanna S, et al, STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989–1002.

115. Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2023;381:e074068.

116. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221–2232.

117. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. *Nat Rev Cardiol*. 2023;20(7):463–474.

118. Duan K, Yan X, Gao Z, Hou Y, Lv X, Song G. Effect of glucagon-like peptide-1 receptor agonists on fat distribution in patients with type 2 diabetes: a systematic review and meta-analysis. *J Diabetes Investig*. 2022;13(7):1149–1160.

119. Wittgrove AC, Clark GW, Tremblay LJ. Laparoscopic gastric bypass, Roux-en-Y: preliminary report of five cases. *Obes Surg*. 1994;4(4):353–357.

120. Sjostrom L, Narbro K, Sjostrom CD, et al, Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741–752.

121. Doumouras AG, Wong JA, Paterson JM, et al. Bariatric surgery and cardiovascular outcomes in patients with obesity and cardiovascular disease: a population-based retrospective cohort study. *Circulation*. 2021;143(15):1468–1480.

122. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;72(14):1677–1749.

123. Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. *N Engl J Med*. 2017;377(1):41–51.

124. Kober L, Thune JJ, Nielsen JC, et al, DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375(13):1221–1230.

125. Sabbag A, Suleiman M, Laish-Farkash A, et al, Israeli Working Group of Pacing and Electrophysiology. Contemporary rates of appropriate shock therapy in patients who receive implantable device therapy in a real-world setting: from the Israeli ICD Registry. *Heart Rhythm*. 2015;12(12):2426–2433.

126. Chandon P, Wansink B. Does food marketing need to make us fat? A review and solutions. *Nutr Rev*. 2012;70(10):571–593.

127. Ello-Martin JA, Ledikwe JH, Rolls BJ. The influence of food portion size and energy density on energy intake: implications for weight management. *Am J Clin Nutr*. 2005;82(suppl 1):236S–241S.

128. Bianchettin RG, Lavie CJ, Lopez-Jimenez F. Challenges in cardiovascular evaluation and management of obese patients: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2023;81(5):490–504.

129. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804–814.

130. Havmoeller R, Reinier K, Teodorescu C, et al. Elevated plasma free fatty acids are associated with sudden death: a prospective community-based evaluation at the time of cardiac arrest. *Heart Rhythm*. 2014;11(4):691–696.

131. Jouven X, Charles MA, Desnos M, Ducimetiere P. Circulating nonesterified fatty acid level as a predictive risk factor for sudden death in the population. *Circulation*. 2001;104(7):756–761.

132. Pilz S, Scharnagl H, Tiran B, et al. Elevated plasma free fatty acids predict sudden cardiac death: a 6.85-year follow-up of 3315 patients after coronary angiography. *Eur Heart J*. 2007;28(22):2763–2769.

133. Holmstrom L, Pylkas K, Tervasmaki A, et al. Genetic contributions to the expression of acquired causes of cardiac hypertrophy in non-ischemic sudden cardiac death victims. *Sci Rep*. 2021;11(1):11171.

134. Ichikawa Y, Kitagawa K, Chino S, et al. Adipose tissue detected by multislice computed tomography in patients after myocardial infarction. *J Am Coll Cardiol Img*. 2009;2(5):548–555.

135. Raney AR, Saremi F, Kenchaiah S, et al. Multidetector computed tomography shows intramyocardial fat deposition. *J Cardiovasc Comput Tomogr*. 2008;2(3):152–163.

136. Lorenz M, Lawson F, Owens D, et al. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovasc Diabetol*. 2017;16(1):6.

137. Al-Sadawi MA, Aslam FM, Tao M, et al. Effects of GLP-1 agonists on mortality and arrhythmias in patients with type II diabetes. *Int J Cardiol Heart Vasc*. 2023;47:101218.

138. Wu S, Lu W, Chen Z, Dai Y, Chen K, Zhang S. Association of glucagon-like peptide-1 receptor agonists with cardiac arrhythmias in patients with type 2 diabetes or obesity: a systematic review and meta-analysis of randomized controlled trials. *Diabetol Metab Syndr*. 2022;14(1):195.

139. Narayanan K, Reinier K, Uy-Evanado A, et al. Frequency and determinants of implantable cardioverter defibrillator deployment among primary prevention candidates with subsequent sudden cardiac arrest in the community. *Circulation*. 2013;128(16):1733–1738.

140. Waks JW, Sitlani CM, Soliman EZ, et al. Global electric heterogeneity risk score for prediction of sudden cardiac death in the general population: the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation*. 2016;133(23):2222–2234.

141. Holmstrom L, Chugh H, Nakamura K, et al. An ECG-based artificial intelligence model for

assessment of sudden cardiac death risk. *Commun Med (Lond)*. 2024;4(1):17.

142. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375(10):919–931.

143. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2016;194(5):613–620.

144. Sanchez-de-la-Torre M, Sanchez-de-la-Torre A, Bertran S, et al, Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020;8(4):359–367.

145. Ball K, Crawford D. Socioeconomic status and weight change in adults: a review. *Soc Sci Med*. 2005;60(9):1987–2010.

146. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315(21):2284–2291.

147. Reinier K, Thomas E, Andrusiek DL, et al, Resuscitation Outcomes Consortium Investigators. Socioeconomic status and incidence of sudden cardiac arrest. *CMAJ*. 2011;183(15):1705–1712.

148. Reinier K, Sargsyan A, Chugh HS, et al. Evaluation of sudden cardiac arrest by race/ethnicity among residents of Ventura County, California, 2015-2020. *JAMA Netw Open*. 2021;4(7):e2118537.

149. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC Health Promotion Series. *J Am Coll Cardiol*. 2018;72(13):1506–1531.

150. Vigmond EJ, Efimov IR, Rentschler SL, Coronel R, Boukens BJ. Fractionated electrograms with ST-segment elevation recorded from the human right ventricular outflow tract. *HeartRhythm Case Rep*. 2017;3(11):546–550.

151. de Bakker JM, van Capelle FJ, Janse MJ, et al. Slow conduction in the infarcted human heart: 'zigzag' course of activation. *Circulation*. 1993;88(3):915–926.

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